

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
14 June 2001 (14.06.2001)

PCT

(10) International Publication Number
WO 01/41564 A2

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- (21) International Application Number: PCT/GB00/04723
- (22) International Filing Date:
11 December 2000 (11.12.2000)
- (25) Filing Language: English
- (26) Publication Language: English
- (30) Priority Data:
9929192.4 10 December 1999 (10.12.1999) GB
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- (81) Designated States (*national*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.
- (84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).
- Published:
— Without international search report and to be republished upon receipt of that report.
- For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.



WO 01/41564 A2

(54) Title: COMPOSITIONS FOR REDUCING OR ELIMINATING HOUSE MITE INFESTATIONS

(57) Abstract: The invention relates to a composition suitable for reducing or eliminating house dust mite infestation, the composition comprising a biocidal agent and a miticide.

COMPOSITIONS FOR REDUCING OR ELIMINATING
HOUSE MITE INFESTATIONS

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This invention relates to compositions for reducing or eradicating house mite infestation.

Background of the Invention

10 Over the past few years, there has been a considerable increase in the incidence of asthma in both adults and children. In many cases, the onset of asthma can be linked to environmental allergens and, in particular, can often be caused by an allergic reaction to house dust mites. House dust mites are small arthropods, typically about 0.25 to 0.33 mm long, and a number of such arthropods have been found in house dust. These include *Dermatophagoides pteronyssinus*, *D. farinae*, *Hirstia*
15 *domicola*, *Malayoglyphus inter medius* and *Euroglyphus mayeni*. Of these, *Dermatophagoides pteronyssinus* has been particularly associated with the incidence of asthma. It is believed that the allergic reaction is triggered by allergens present in the faecal pellets produced by the mites.

The typical diet of a house dust mite can include human skin scales, fungi growing on the skin,
20 moulds, insect bodies or fragments, pollen grains, bacteria, plant material and household dust containing these items. Mites tend to be found in greater numbers in soft furnishings such as carpets and bedding, and in environments which have relatively high humidity. It has been demonstrated that the faecal pellets that mites egest can accumulate in furnishings such as carpets and bedding are allergenic. Such pellets can become airborne when dust is disturbed by such activities as vacuuming or
25 dusting and consequently are inhaled, leading in many cases to the allergic reaction.

A variety of different methods have been used to control or reduce house mite infestation. For example physically encasing bedding and pillows with a relatively impermeable but breathable material such as rubber or a vinyl plastics material can prevent infestation of soft furnishings such as pillows
30 and other bedding. Washing techniques, particularly hot water washing at temperatures of 60°C or higher can also be effective in reducing mite numbers. Dry cleaning also kills mites, and is relatively effective at physically removing dust from items such as bedding.

- 2 -

General heating may also be applied, for example in steam treatment of carpets, during washing cycles, by direct sunlight exposure, by autoclaving, or by dry heating, for example by electric blankets. Freezing has also been used as a means of killing mites, although this is much less practical in a domestic environment. The use of vacuum cleaners to remove mites has also been attempted, but
5 this tends to have relatively little effect on overall numbers.

In addition to the physical methods of mite control, chemical methods have also been used. Thus, certain acaricidal substances are commonly used in the treatment of mites. One example is benzyl benzoate which is marketed under the trade names "Acarosan", "Allerbiocide" and "Artilin".
10 Benzyl alcohol has also been used.

Other chemicals that have acaricidal properties are pyrethrum analogs and pyrethroids, organophosphates, pyridazinones and essential plant oils. Fungicides such as natamycin have also been used to kill mites.
15

Despite the foregoing, there remains a general need for improved methods of the management of mites and in particular a general need for methods of reducing mite infestation in a domestic or industrial context thereby to reduce the incidence of allergic asthma caused by mites.

20 The present invention is predicated on the fact that a substantial part of the diet of house mites consists of bacteria, as well as moulds and fungi and that by reducing the numbers of such microorganisms, thereby depriving the mites of a substantial source of food, it should be possible to bring about elimination of house mites much more easily and with the use of lower concentrations of miticidal agents.

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Summary of the Invention

Accordingly, in a first aspect, the present invention provides a composition for reducing or eliminating house dust mite infestation, the composition comprising a biocidal agent and a miticide.

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The biocidal agent is typically an antimicrobial agent having activity against bacteria and preferably also fungi. The biocidal agent is most preferably non-toxic to mammals and in particular to humans at the concentrations needed to achieve the antimicrobial effect.

- 3 -

In another aspect, the invention provides a method of reducing or eradicating house dust infestation, which method comprises subjecting a locus infested with house dust mites to treatment with a composition as hereinbefore defined.

5 Examples of anti-microbial agents for use in the compositions of the present invention include amphoteric compounds, iodophores, phenolic compounds, quaternary ammonium compounds, hypochlorites and nitrogen-based heterocyclic antibacterial compounds.

10 Examples of miticidal agents include insecticidal compounds such as carbamate pesticides, chlorinated pesticides, organophosphorus pesticides and pyrethroid pesticides.

Antimicrobial Agents

15 Examples of amphoteric antimicrobial compounds include long chain N-alkyl derivatives of amino acids such as glycine, alanine and beta-amino butyric acid, particular examples being dodecyl beta-alanine, dodecyl beta-aminobutyric acid, dodecylamino-di(aminoethylamino)-glycine and N-(3-dodecylamino)propyl glycine.

20 The term iodophores as used herein refers to complexes of iodine or triiodide with a carrier, such as a neutral polymer. The carrier typically is one which increases the solubility of iodine in water, provides a sustained release of the iodine and reduces the equilibrium concentrations of free iodine. Examples of polymeric carriers from which iodophore compositions can be made include polyvinylpyrrolidone, polyether glycols such as polyethylene glycols; polyvinyl alcohols, polyacrylates, polyamides, polyoxyalkylenes, and polysaccharides. A preferred iodophore is povidone iodine, in which the carrier is polyvinylpyrrolidone.

25 Examples of quaternary ammonium compounds include compounds of the general formula $R_1R_2N^+R_3R_4 X^-$ wherein one or two of the R groups are alkyl chains optionally substituted by an aryl group, or optionally interrupted by an aryl group or a heteroatom such as oxygen, and the other R groups are the same or different and are C_1 - C_4 alkyl groups and in particular methyl groups. Examples of classes of quaternary ammonium compounds within this general formula include benzalkonium halides, aryl ring substituted benzalkonium halides such as ethyl-substituted benzalkonium halides (e.g. Barquat 4250 available from Lonza), and twin chain quaternary ammonium compounds such as dialkyldimethylammonium compounds wherein the two non-methyl alkyl groups are selected from

- 4 -

medium and long chain alkyl groups such as octyl groups and dodecyl groups. Examples of quaternary ammonium compounds in which an alkyl group R contains an oxygen heteroatom include domiphen bromide, benzethonium chloride and methylbenzethonium chloride.

- 5 Other examples of quaternary ammonium compounds include alkylpyridinium compounds such as cetylpyridinium chloride, and bridged cyclic amino compounds such as the hexaminium compounds, e.g. N-(3-chlorallyl)hexaminium chloride.

- Examples of phenolic compounds include methyl, halo- and aryl substituted phenolic
10 compounds such as 2-phenylphenol, 2-benzyl-4-chlorophenol, 2-cyclopentyl-4-chlorophenol, 4-t-
amylphenol, 4-t-butylphenol, 4-chloro-2-pentylphenol, 6-chloro-2-pentylphenol, p-chloro-meta-xyleneol,
2,4,4'-trichloro-2'-hydroxydiphenol, thymol (2-i-propyl-3-methylphenol), chlorothymol, 3-methyl-4-
chlorophenol, 2,6-dichloro-4-n-alkylphenols, 2,4-dichloro-meta-xyleneol, 2,4,5-trichlorophenol and 2-
benzyl-4-chlorophenol.

15

Examples of hypochlorites include alkali-metal and alkaline earth metal hypochlorites such as lithium hypochlorite, sodium hypochlorite, potassium hypochlorite, calcium hypochlorite, and chlorinated trisodium phosphate and their various hydrates.

- 20 Other chlorine-containing or chlorine-releasing agents include chlorine dioxide and its precursors, as well as 4-sulphondichloramido benzoic acid (halazone), 1,3-dichloro-5,5-dimethylhydantoin (halane), and various chloroisocyanuric acid derivatives.

- Examples of nitrogen-containing anti-bacterial agents include pyridine derivatives such as 4-
25 pyridine carboxylic acid hydrazide, sodium 2-pyridinethiol-1-oxide (Sodium Omadine™), bis-(2-
pyridylthio)zinc 1,1'-dioxide (Zinc Omadine), triazoles and imidazoles such as 2-(4-thiazolyl)
benzimidazole (Metasol TK-100); isothiazolinones such as 12-benzisothiazoline-3-one (Proxcel™); 2-
n-octyl-4-isothiazolin-3-one (Kathon™), 2-bromo-2-nitro-1,3-propanediol (bromonopol™), 3-
trifluoromethyl-4,4'-dichlorocarbonyl (Irgasan™), quinacrine HCl (Atabrine™), ciprofloxacin and
30 nalidixic acid and its various derivatives.

In a preferred embodiment, the antimicrobial agent comprises a combination of a benzalkonium compound such as a benzalkonium halide and an isothiazolinone compound.

- 5 -

The isothiazolinone can be, for example, a substituted or unsubstituted isothiazolin-3-one, and particular examples of substituted isothiazolin-3-ones are these bearing a substituent such as halogen (e.g. a chloro-substituent) in the 5-position.

5 Advantageously the isothiazolinone is selected from 5-chloro-2-methyl-4-isothiazolin-3-one, or 2-methyl-4-isothiazolin-3-one, or a mixture thereof. Preferably the isothiazolinone is a mixture of the two aforesaid isothiazolinones.

10 Examples of benzalkonium halides include N-alkyl-N-benzyl dimethylammonium chloride.

The N-alkyl group typically contains from 12 to 16 carbon atoms and a particularly preferred benzalkonium compound is a mixture of N-C₁₄ alkyl-N-benzyl-dimethylammonium chloride, N-C₁₂ alkyl-N-benzyl-dimethylammonium chloride and N-C₁₆ alkyl-N-benzyl-dimethylammonium chloride, most preferably in the ratio 50:40:10.

15 The weight ratio of the isothiazolinone to benzalkonium halide in the composition can vary, for example from about 1:500 to about 1:1. More usually, the weight ratio will lie in the range from about 1:300 to about 1:3. For example in one embodiment the weight ratio lies between about 1:30 and about 1:40. In another embodiment, the weight ratio lies between about 1:3 and 1:4.

20 The term "weight ratio" as used herein refers to the dry weights of the component compounds.

Miticidal Agents

25 The miticide can be any one of a wide range of insecticidal or acaricidal agents.

Particular examples of insecticides which may be used as the miticides in the compositions of the invention are the compounds listed on pages 1429 to 1441 of *Martindale, The Extra Pharmacopoeia, 31st Edition, Publ. Royal Society of Great Britain, 1996*.

30 Examples of pyrethroid compounds include bioallethrin, cyfluthrin, cyhalothrin, cypermethrin, deltamethrin, esdepallethrine, flumethrin, permethrin, phenothrin, resmethrin and tetramethrin. Preferred pyrethroids include phenothrin and cyhalothrin, particularly cyhalothrin. A major advantage

- 6 -

of the pyrethroids is that whilst they have good activity against insects and mites, they have very low mammalian toxicity.

Preferred Combinations

5 In a preferred embodiment of the invention, the composition contains an antimicrobial agent comprising a benzalkonium halide and an isothiazolinone, and a miticidal component comprising a pyrethroid, particularly cyhalothrin.

10 In a particularly preferred embodiment, the invention provides a composition comprising the antimicrobial composition "Bactiguard" (available from Liquid Technology Limited, Woolston, Warrington, Cheshire), and the pyrethroid cyhalothrin.

The compositions of the present invention can be used to treat air filters, for example filters of the type used in air-conditioning and ventilation systems. Filter membranes used in such systems typically are formed from , polyester, polypropylene, paper or various washable materials, e.g. washable textiles and can be treated with liquid compositions according to the present invention to impart miticidal properties to the filter membranes. The liquid compositions of the invention can be sprayed on to the filter in the form of an aqueous solution, the water then being allowed to evaporate. However, it is most preferred to impregnate the filter media throughout its depth or thickness by incorporating the active components of the compositions into the filter media during manufacture. Filter media such as filter membranes, e.g. air filters and vacuum cleaner filters, impregnated or coated with a miticide such as a pyrethroid, e.g. cyhalothrin (with or without the presence of an anti-microbial agent), represent a further aspect of the invention.

25 The compositions of the invention can be used to treat, e.g. coat or otherwise impregnate, articles and materials in locations (loci) where house dust mites are found. In addition to the air filter media disclosed above, examples of articles that can be impregnated or coated with the compositions include walls, floors, ceilings and other surfaces, articles of cloth or textiles such as carpets, upholstery, covers, bedding and mattresses.

30

Implements, apparatus or other articles or materials used in the cleaning of houses may also be impregnated or coated with the compositions of the invention. Examples of such articles include cloths, dusters, dust mops, feather dusters, brushes, brooms, carpet sweepers, vacuum cleaner components

- 7 -

such as filters, collection bags and collection chambers, hoses, vacuum cleaner tools, vacuum cleaner brushes and bristles, clothes brushes, hair brushes, combs and carpet beaters.

The compositions of the invention can also be formulated together with detergent compositions
5 for application to carpets, mats, floors and other surfaces within buildings, as well as laundry detergent compositions and fabric conditioners.

Carpet protection coatings intended to prevent staining or reduce wear and tear on carpets may
also be treated with the compositions. In this way, the miticidal composition becomes a permanent or
10 semi-permanent component of the surface coating of the carpet.

The compositions can also be presented as textile treatment compositions, for example for
application to laundry, particularly bedding, after the wash cycle has been completed.

15 The compositions of the invention may also be incorporated into surface coating material such
as paints. For example, the compositions may be incorporated into standard paint bases, e.g. oil-based
paints or emulsion paints, or water-based paints, epoxy resin paints and floor screeds, and polyurethane
and elastomeric co-polymer coatings, and the resulting used to treat surfaces in areas where it is desired
to reduce or eliminate house-dust mite infestation contamination. For example, paints incorporating the
20 compositions of the present invention may be used to treat the inner surfaces of air conduits and pipes
used in air-conditioning and ventilation systems, and components of air-treatment systems such as air-
conditioning systems, eg. filters, grilles, tubes, components of fans, air inlets and outlets and ducting.

Accordingly, in a further aspect, the invention provides an article containing, coated with or
25 impregnated with a composition as hereinbefore defined.

The compositions of the invention are advantageously formulated in a carrier liquid for
application to an article by, for example, spraying, dipping or painting. The liquid carrier can be an
aqueous or non-aqueous carrier. In one preferred embodiment, the carrier comprises a non-aqueous
30 carrier liquid, and examples of such liquids include polar carrier liquids such as glycols, for example
alkylene and polyalkylene glycols, e.g. diethylene glycol, hexylene glycol and polyethylene glycol. A
preferred glycol is diethylene glycol.

- 8 -

For liquid compositions, the antimicrobial agent will typically be present in a concentration of up to 20% (w/w), for example 0.1% to 20%, preferably at least 1%, e.g. 1% to 15%, more usually up to 10%, e.g. 5% to 10%, for example approximately 8%.

- 5 The miticidal agent will typically be present in a concentration of up to 5% (w/w) of the total weight of the composition, more typically less than 3%, for example less than 2%, preferably less than 1%, e.g. 0.1% or more, for example approximately 0.75%.

10 The compositions can also be presented in solid form, for example as dusts or powders, or as tablets or pellets for dissolving in a solvent such as water.

The compositions can, if desired, be formulated as personal care products, such as shampoos, deodorants, body sprays, roll-ons, creams and lotions. The methods of preparing such formulations are well known and details need not be repeated here.

15

- The compositions and articles of the present invention, in addition to having activity against mites, also have activity against a wide range of gram positive and gram negative bacteria, such as *Bacillus cereus*, *Bacillus subtilis*, *Brevibacterium ammoniagenes*, *Brucella abortus*, *Klebsiella pneumoniae*, *Lactobacillus casei*, *Proteus vulgaris*, *Listeria monocytogenes*, *Pseudomonas aeruginosa*,
20 *Salmonella gallinarum*, *Salmonella typhosa*, *Staphylococcus aureus*, *Streptococcus faecalis*, *Flavobacterium* species, *Bacillus* species, *Escherichia* species, *Aeromonas* species, *Achromobacter* species and *Alcaligenes* species; fungi such as *Cephalosporium* species, *Cladosporium* species, *Fusarium* species, *Paecilomyces* species, *Penicillium* species, *Streptomyces* species, *Trichophyton interdigitale*, *Chaetorarium globesum*, *Aspergillus niger*, and *Ceniphora puteana*, yeasts such as
25 *Monilia albicans* and *Saccharomyces cerevisiae*, and algae such as *Chlorella pyrenoidosa* and *Anabaena cylindrica*.

- Without wishing to be bound by any theory, it is therefore envisaged that the compositions of the invention will act by killing the dust mites quickly with the further effect of killing bacteria and
30 fungi and other microbes known to form part of the diet of the mites and that depriving the mites of their usual food sources will enhance and prolong the killing effect of the miticidal components of the compositions, while at the same time providing ongoing activity against the bacteria once the mites have been eradicated.

- 9 -

Furthermore, by impregnating or coating air filters with the compositions of the invention, and hence killing mites entrained in the air before they can enter a room, establishment or re-establishment of a mite population in the room can be prevented or substantially hindered.

- 5 The preparation and properties of the compositions and articles of the present invention will now be illustrated, but not limited, by the following examples.

EXAMPLE 1

- 10 The antimicrobial activity of a composition of the invention was compared with a control composition containing an antimicrobial agent but no miticide. In this example, the test composition was a "Bactiguard" (TM) solution (obtainable from Liquid Technology Limited, Woolston, Warrington, Cheshire, UK) containing benzalkonium chloride, 5-chloro-2-methyl-4-isothiazolin-3-one and 2-methyl-4-isothiazolin-3-one, to which had been added the pyrethroid cyhalothrin. The "control"
- 15 solution was the "Bactiguard" solution without the pyrethroid. The Test and Control solutions were used to impregnate discs of filter material.

- The Control and Test samples were challenged with diluted overnight broth cultures of *E. coli* (*E. coli* NCTC 10418 1.3×10^5 cfu/ml), 0.1 ml drops of the bacterial suspension being pipetted onto
- 20 2.5 cm² sections of the filters. The filters were kept at room temperature throughout the trial. At the required times of: 0, 1, 2, 5, 10, 30 minutes and 1, 2, 3, 4, 5 and 6 hours, the filters with the bacterial suspension were placed into 10 ml phosphate buffered solution with 0.5% Tween (RTM) and shaken gently to release the bacteria into the solution. The elution was pipetted onto Standard Plate Count Agar using a spiral plater. Incubation was carried out at $30 \pm 1^\circ\text{C}$ for 48 ± 2 hours and the total number
- 25 of colonies was counted and calculated. The results demonstrated that within one minute, the number of colony forming units of *E. coli* had declined from 133333 to 0, thereby demonstrating that the pyrethroid did not disrupt the action of the antimicrobial agent in eradicating bacteria.

EXAMPLE 2

- 30 Miticidal Activity of the Compositions

Four samples of filter media, two of which had been impregnated with the Test composition of Example 1, and two of which had been impregnated with the Control solution, were each exposed to 50

- 10 -

house dust mites. In the case of the two filter media samples treated with the test compositions, all of the mites were dead within 4 hours. The sample treated with the highest concentration of the Test solution achieved 94.66 mortality after the first hour, and 100% mortality after the second hour, with no re-colonisation within 24 hours.

5

EXAMPLE 3

A composition containing "Bactiguard" (TM) solution and the pyrethroid cyhalothrin as described in Example 1 is diluted with water to a strength of 4:1 or 8:1 (water:anti-bacterial agent) to provide a solution which is then used to dip or spray a conventional polyester filter element of the type
10 manufactured by Libeltx of Marialoopsteenweg, 51, B-8760 Mevlebeke, Belgium.

EXAMPLE 4

A neat diethylene glycol solution of the anti-bacterial agent/cyhalothrin combination described in Example 1 is diluted 4:1 or 8:1 (water:anti-bacterial agent/cyhalothrin) and the resulting aqueous
15 composition is added to a conventional paint base at a concentration of 10cm³ per 100cm³ of paint. The resulting anti-bacterial paint is used to coat the conduits and grilles of an air-conditioning system.

EXAMPLE 5

A neat diethylene glycol solution of the anti-bacterial/miticidal combination described in
20 Example 1 is mixed with ethylenevinylacetate (EVA) pellets in an amount corresponding to 5% by weight of the total weight of the solution/pellet mixture in such a way as to ensure thorough coating of the pellets with the mixture. The coated pellets are then introduced into the hopper of a conventional injection moulding machine and moulded into a variety of shapes and sizes. Articles formed by this method are found to have excellent bactericidal and miticidal properties, over a prolonged period, e.g.
25 several months.

EXAMPLE 6

An anti-bacterial composition analogous to the compositions described in Examples 1 to 4 is
30 made up in diethylene glycol to a solution strength of 5% (W/V) from chloroxyleneol rather than the isothiazolinones..

The resulting neat diethylene glycol solution is then used in the manufacture of EVA articles,

- 11 -

or in paint bases, or as spraying or dipping solutions, as described in Examples 3 to 5.

EXAMPLE 7

5 The bactericidal/miticidal composition of Example 1 solution is diluted with water to give a concentration (w/v) of the active ingredients of 5% and the resulting solution is used to dip or spray household items such as carpets, soft furnishings and curtains. The treated item is allowed to dry and thereafter exhibits excellent bactericidal and miticidal properties.

10 It will readily be apparent that numerous modifications and alterations could be made to the exemplified composition and article without departing from the principles underlying the invention, and all such modifications and alterations are intended to be within the scope of this application.

- 12 -

CLAIMS

1. A composition for reducing or eliminating house dust mite infestation, the composition comprising a biocidal agent and a miticide.
- 5 2. A composition according to claim 1 wherein the biocidal agent is an antimicrobial agent having activity against bacteria.
- 10 3. A composition according to claim 2 wherein the antimicrobial agent is selected from amphoteric compounds, iodophores, phenolic compounds, quaternary ammonium compounds, hypochlorites and nitrogen-based heterocyclic antibacterial compounds.
- 15 4. A composition according to any one of the preceding claims wherein the miticidal agent is selected from carbamate pesticides, chlorinated pesticides, organophosphorus pesticides and pyrethroid pesticides.
5. A composition according to claim 4 wherein the miticidal agent is a pyrethroid.
- 20 6. A composition according to any one of the preceding claims wherein the antimicrobial agent is a quaternary ammonium compound.
- 25 7. A composition according to claim 6 wherein the quaternary ammonium compound is a compound of the general formula $R_1R_2N^+R_3R_4 X^-$ wherein or one or two of the R groups are alkyl chains optionally substituted by an aryl group, or optionally interrupted by an aryl group or a heteroatom such as oxygen, and the other R groups are the same or different and are C_1-C_4 alkyl groups and in particular methyl groups.
- 30 8. A composition according to claim 7 wherein the quaternary ammonium compound is a benzalkonium halide.
9. A composition according to any one of claims 6 to 8 wherein the antimicrobial agent comprises a combination of a benzalkonium compound and an isothiazolinone compound.
10. A composition according to any one of the preceding claims wherein the miticidal compound is

- 13 -

a pyrethroid selected from bioallethrin, cyfluthrin, cyhalothrin, cypermethrin, deltamethrin, esdepallethrine, flumethrin, permethrin, phenothrin, resmethrin and tetramethrin.

11. A composition according to any one of the preceding claims which contains an antimicrobial agent comprising a benzalkonium halide and an isothiazolinone, and a miticidal component comprising a pyrethroid such as cyhalothrin.
5
12. An article containing, coated with or impregnated with a composition as defined in any one of the preceding claims.
10
13. An article according to claim 12 which is an air filter or vacuum cleaner filter.
14. An article according to claim 12 which is selected from walls, floors, ceilings and other surfaces, articles of cloth or textiles such as carpets, upholstery, covers, bedding and mattresses; articles or materials used in the cleaning of houses such as cloths, dusters, dust mops, feather dusters, brushes, brooms, carpet sweepers, vacuum cleaner components such as filters, collection bags and collection chambers, hoses, vacuum cleaner tools, vacuum cleaner brushes and bristles, clothes brushes, hair brushes, combs and carpet beaters.
15
15. An article comprising filter media such as filter membranes, e.g. air filters and vacuum cleaner filters, impregnated or coated with a miticide such as a pyrethroid, e.g. cyhalothrin.
20
16. A method of reducing or eradicating house dust infestation, which method comprises subjecting a locus infested with house dust mites to treatment with a composition as defined in any one of claims 1 to 12.
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(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
14 June 2001 (14.06.2001)

PCT

(10) International Publication Number
WO 01/41564 A3

- (51) International Patent Classification⁷: **A01N 53/00**, 43/80, 33/12, 31/08, 47/10, 57/00, 59/12, 31/16, 31/12, 59/00 // (A01N 53/00, 59:12, 59:00, 43:80, 33:12, 31:16, 31:12, 31:08) (A01N 57/00, 59:12, 59:00, 43:80, 33:12, 31:16, 31:12, 31:08) (A01N 47/10, 59:12, 59:00, 43:80, 33:12, 31:16, 31:12, 31:08)
- (21) International Application Number: PCT/GB00/04723
- (22) International Filing Date:
11 December 2000 (11.12.2000)
- (25) Filing Language: English
- (26) Publication Language: English
- (30) Priority Data:
9929192.4 10 December 1999 (10.12.1999) GB
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- (81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.
- (84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).
- Published:
— with international search report
- (88) Date of publication of the international search report:
10 January 2002
- For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 01/41564 A3

(54) Title: COMPOSITIONS FOR REDUCING OR ELIMINATING HOUSE MITE INFESTATIONS

(57) Abstract: The invention relates to a composition suitable for reducing or eliminating house dust mite infestation, the composition comprising a biocidal agent and a miticide.

INTERNATIONAL SEARCH REPORT

Int. l. Application No PCT/GB 00/04723		
A. CLASSIFICATION OF SUBJECT MATTER IPC 7 A01N53/00 A01N43/80 A01N33/12 A01N31/08 A01N47/10 A01N57/00 A01N59/12 A01N31/16 A01N31/12 A01N59/00 //(A01N53/00, 59:12, 59:00, 43:80, 33:12, 31:16, 31:12, 31:08), According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) IPC 7 A01N Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched Electronic data base consulted during the international search (name of data base and, where practical, search terms used) EPO-Internal, WPI Data		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
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<div style="display: flex;"> <div style="flex: 1;"> <p>* Special categories of cited documents :</p> <p>*A* document defining the general state of the art which is not considered to be of particular relevance</p> <p>*E* earlier document but published on or after the international filing date</p> <p>*L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>*O* document referring to an oral disclosure, use, exhibition or other means</p> <p>*P* document published prior to the international filing date but later than the priority date claimed</p> </div> <div style="flex: 1;"> <p>*T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>*X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone</p> <p>*Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>*8* document member of the same patent family</p> </div> </div>		
Date of the actual completion of the international search	Date of mailing of the international search report	
7 March 2001	05/07/2001	
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Authorized officer Klaver, J	

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Int. l. Application No
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A. CLASSIFICATION OF SUBJECT MATTER IPC 7 (A01N57/00, 59:12, 59:00, 43:80, 33:12, 31:16, 31:12, 31:08), (A01N47/10, 59:12, 59:00, 43:80, 33:12, 31:16, 31:12, 31:08)		
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B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols)		
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* Special categories of cited documents : *A* document defining the general state of the art which is not considered to be of particular relevance *E* earlier document but published on or after the international filing date *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) *O* document referring to an oral disclosure, use, exhibition or other means *P* document published prior to the international filing date but later than the priority date claimed *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art. *&* document member of the same patent family		
Date of the actual completion of the international search		Date of mailing of the international search report
7 March 2001		
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040. Tx. 31 651 epo nl. Fax: (+31-70) 340-3016		Authorized officer Klaver, J

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Int. l. Application No
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